II. Remarks

Claims 1, 2, 4, 5, 7-12 and 39-53 are pending. New claim 53 has been added.

A. Obviousness-type Double Patenting Rejection

In the instant Office Action, a nonstatutory obviousness-type double patenting rejection has been maintained for claims 1, 2, 4-5, 7-12 and 51-52 as being unpatentable over claims 20, 21 and 23-27, and for claims 39-42 and 46-50 as being unpatentable over claims 25-27 of U.S. Patent No. 6,103,219. An obviousness-type double patenting rejection has also been maintained against claims 39-42 and 46-50 as being unpatentable over claims 19, 20, 24, 30, 32 and 33 of U.S. Patent No. 6,746,693.

These rejections were maintained because the New Terminal Disclaimers have not been approved. The Examiner has not indicated a deficiency in the Terminal Disclaimers. Therefore, it is believed that no further action is required by Applicants with respect to this rejection. If it is determined that action is required by Applicants, it is respectfully request that Examiner notify the undersigned to comply with any deficiencies. Applicants believe the submission of the Terminal Disclaimers on January 9, 2009 obviates all outstanding obviousness-type double-patenting rejections, and respectfully request approval of the Terminal Disclaimers and withdrawal of these rejections.

B. 35 U.S.C. §103 Rejections

In the Office Action, the Examiner maintained the rejections of claims 1, 2, 4, 5, 7-12 and 39-52 under 35 U.S.C. §103(a) as being unpatentable over United States Patent No. 4,910,023 to Botzolakis et al. ("Botzolakis"). At page 15 of the Office Action, the Examiner stated "*Botzolakis teaches '... microcrystalline cellulose with the colloidal silicon dioxide absorbs onto the drug particles'' (Abstract, Col. 2, lines 11-17). Therefore, the intimate association of*

microcrystalline cellulose and silicon dioxide is implicit." At page 16 of the Office Action, the Examiner then concluded that it would have been obvious to compare the results of: a) a slurry of microcrystalline cellulose colloidal silicon dioxide and maltasting drug with b) maltasting drug mixed with preformed microcrystalline cellulose and colloidal silicon dioxide, in order to optimize taste masking of the maltasting drug.

In response, these rejections are respectfully traversed. Independent claims 1,39 and 53 are set forth below.

> *Claim 1: A method for preparing a tablet, consisting essentially of the steps of:*
>
> *forming an aqueous slurry containing a mixture of microcrystalline cellulose in the form of a wet cake and silicon dioxide having a particle size from about 1 nm to about 100 μm;*
>
> *drying said slurry to obtain an excipient comprising a plurality of agglomerated particles of microcrystalline cellulose in intimate association with said silicon dioxide, the amount of silicon dioxide being from about 0.1% to about 20% relative to the amount of microcrystalline cellulose, by weight;*
>
> *then mixing a moisture-sensitive active ingredient with said excipient in a ratio from about 1:99 to about 99:1 to obtain a mixture; and compressing said mixture into a tablet.*

Claim 39: A method for preparing a tablet, consisting essentially of the steps of:
(a) forming an aqueous slurry of microcrystalline cellulose in the form of wet cake;
(b) forming an aqueous slurry of silicon dioxide having a particle size of from about 1 nm to about 100 μm;
(c) separately introducing said microcrystalline cellulose slurry and said silicon dioxide slurry separately into a drying apparatus for combination therein, to obtain an excipient comprising a plurality of agglomerated particles of microcrystalline cellulose in intimate association with said silicon dioxide, the amount of silicon dioxide being from about 0.1% to about 20% relative to the amount of microcrystalline cellulose, by weight; then
(d) mixing a moisture-sensitive active ingredient with said excipient in a ratio of from about 1:99 to about 99:1 to obtain a mixture; and
(e) compressing said mixture into a tablet.

Claim 53. (New): A method for preparing a tablet, consisting essentially of the steps of:
forming an aqueous slurry containing a mixture of microcrystalline cellulose in the form of a wet cake and silicon dioxide having a particle size from about 1 nm to about 100 μm;
drying said slurry to obtain an excipient comprising a plurality of agglomerated particles of microcrystalline cellulose in intimate association with said silicon dioxide, the amount of silicon dioxide being from about 0.1% to about 20% relative to the amount of microcrystalline cellulose, by weight, <u>wherein said excipient is not obtained by wet granulation;</u>
then mixing a moisture-sensitive active ingredient with said excipient in a ratio from about 1:99 to about 99:1 to obtain a mixture; and
compressing said mixture into a tablet. Emphasis added

<u>No Basis for Concluding that Processes in Botzolakis Provide Intimate Association</u>

It is respectfully submitted that the Examiner has provided no evidence or suggestion whatsoever in concluding that the wet granulation process of Botzolakis would provide intimate association between microcrystalline cellulose and colloidal silicon dioxide. The Examiner's

conclusion that intimate association is 'implicit' without providing any reasoning or factual evidence is insufficient to support this rejection. The Botzolakis reference itself provides no explicit or implied foundation as support for the Examiner's conclusion. Furthermore, the Examiner's conclusion is unaccompanied by any evidence in which this improper conclusion could be supported. Therefore, in the absence of any factual basis for this conclusion, removal of the Examiner' rejection is respectfully requested.

The Examiner's Proposed Modification to Botzolakis in Unfounded

It is once again respectfully submitted that the instant claims are directed in part to a process where an excipient comprising microcrystalline cellulose and colloidal silicon dioxide is first made with an aqueous slurry and then dried. After the excipient is dried, it is then combined with a moisture sensitive active ingredient. This process is not taught or suggested by Botzolakis. However, the Examiner has concluded that a person having ordinary skill in the art would take the teachings of Botzolakis directed to (A) a wet granulation process involving a maltasting drug, mixed with microcrystalline cellulose and colloidal silicon dioxide and modify it by (B): (1) removing the maltasting drug from the wet granulate process, (2) drying the wet granulate and (3) adding the maltasting drug back into the dry product. The Examiner's justification is that a person of ordinary skill in the art would compare taste masking of the maltasting drug by processes A and B. Applicant respectfully disagrees. Initially, as set forth above, the Examiner has not provided a basis for concluding that the Botzolakis process would provide for microcrystalline cellulose and colloidal silicon dioxide in intimate association. Additionally, without the perspective of the instant invention, a person having ordinary skill in the art at the time of the invention simply would not make these modifications to Botzolakis. In fact, Botzolakis did not make this modification and the Examiner has failed to provide any examples of such a modification.

Moreover, new independent claim 53 recites a process involving preparing an excipient that specifically excludes wet granulation. As Botzolakis is limited to wet granulation, Applicants respectfully submit that for this additional reason, claim 53 is not obvious over Botzolakis.

Obviousness Rejections of Claims 2 and 40

Regarding claims 2 and 40, the Examiner asserted "*the limitations of colloidal silicon dioxide and wet granulation prior to compression would have been obvious over the colloidal silicon ... and wet granulation prior to compression, as taught by Botzolakis (Col. 3, lines 39-52).*"

This rejection is respectfully traversed. Claims 2 and 40 further recite wet granulating prior to compressing the mixture of (i) the coprocessed excipient particles of microcrystalline cellulose in intimate association with colloidal silicon dioxide and (ii) moisture-sensitive active agent, into a tablet. As set forth at page 27, lines 21-25 of the originally filed specification, a representative wet granulation contemplated by the present invention utilizes a granulation liquid mixed with the dry mass to create a powdery mass that has the consistency of damp snow.

By contrast, Botzolakis describes an allegedly unique wet granulation process which requires a slurry of (i) drug, colloidal silicon dioxide and water in Example 1 and (ii) drug dissolved in water with colloidal silicon dioxide in Example 2.

Applicants note that the Botzolakis process does not form a "pre-manufactured" excipient comprising agglomerated particles of microcrystalline cellulose in intimate association with the silicon dioxide, prior to the addition of a moisture-sensitive active agent, which advantageously protects the moisture-sensitive active, as provided by the subject invention. In other words, the wet granulation step of Botzolakis is used for creating a protective coating of colloidal silicon

dioxide over maltasting drug particles for taste-masking drug particles, not for forming granules for tableting. These are two separate and distinct types of wet granulation steps, and cannot simply be morphed as equivalent. They are not. Therefore, for these additional reasons, the processes involving an additional wet granulation steps recited in claims 2 and 40 are not obvious over Botzolakis. Accordingly, withdrawal of the Examiner's rejection of claims 2 and claim 7 dependent therefrom; and claim 40 and claim 45 dependent therefrom is respectfully requested.

The Examiner also rejected claims 4-5, 41-44 and 51-52 under 35 U.S.C. §103(a) as being unpatentable over Botzolakis in view of United States Patent No. 4,605,666 to Schmidt et al. ("Schmidt"). The Examiner stated "*Botzolakis does not expressly teach spray drying. Schmidt teaches a 'process for preparing a powder ... which is directly compressible into a tablet prepared by spray drying (a) an aqueous slurry of a water-soluble vitamin and a binder, (b) ... an adsorbent and (c) a lubricant (Abstract).*" The Examiner then asserted "*it would have been obvious to one of ordinary skill in the art at the time the invention was made to use the method of making a tablet ... as taught by Botzolakis, vary the addition of a moisture sensitive active ingredient to the slurry containing colloidal silicon dioxide and microcrystalline cellulose during the process of routine optimization, combine it with the process of spray drying to produce a compressible powder, and produce the instant invention.*"

The Examiner's rejection is respectfully traversed. The Examiner has relied on a combination of Botzolakis and Schmidt in a further modified, unsupportable manner to create a new invention of her own design. It is respectfully submitted that the modifications that the Examiner suggests be done in order to combine these references in any meaningful way is simply a fabrication which is not supportable by any factual basis. The Examiner's proposed (combined) process would ignore required steps by Botzolakis making an agglomerate of drug/colloidal silicon dioxide; then adding a new step (varying the addition of another

ingredient) not taught in either reference; then modifying a spray drying step described in Schmidt to produce the invention. The Examiner's recreation does not render the claims in question obvious, but rather is an example of an improper use of hindsight based solely on information provided in Applicants' claims.

Dependent claims 4, 41, 42 and 51 (requiring spray-drying) and dependent claims 5, 43, 44 and 52 (requiring a bulk density of from 0.2 g/ml to about 0.6 g/ml) obvious. The deficiencies set forth above with respect to Botzolakis are reasserted herein. The deficiencies of Botzolakis are not cured by Schmidt. Schmidt alleges a process where a water soluble vitamin is prepared into an aqueous slurry with microcrystalline cellulose that is spray-dried and silicon dioxide and magnesium stearate added to the drying chamber. Both Botzolakis and Schmidt fail to teach or suggest dry agglomerated particles of microcrystalline cellulose in intimate association with silicon dioxide as recited in the instant claims. Additionally, both Botzolakis and Schmidt fails to provide a basis for a person having ordinary skill in the art at the time of the invention to form a "pre-manufactured" excipient comprising a plurality of agglomerated particles of microcrystalline cellulose in intimate association with the silicon dioxide, prior to the addition of a moisture-sensitive active agent, which advantageously protects the moisture-sensitive active, as provided by the subject invention. Therefore, the teachings of Botzolakis combined with Schmidt fail to provide all of the limitations of claims 4-5, 41-44 and 51-52. Accordingly, withdrawal of the Examiner's rejection is respectfully requested.

III. Conclusion

In view of the arguments presented, it is respectfully submitted that the present application is now in condition for allowance. An early and favorable action on the merits is earnestly solicited. According to currently recommended Patent Office policy, the Examiner is specifically authorized to contact the undersigned in the event that a telephonic interview will advance the prosecution of the application. A Request for Continued Examination, a request for a two-month extension of time to reply to the Office Action along with an authorization for the Commissioner to charge the undersigned's Attorney Deposit Account the requisite fees is also submitted herewith.

Respectfully submitted,
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